Remarks

Claims 1-21 were pending in the subject application. By this Amendment, claims 1-9 have been cancelled and new claims 22-49 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Claims 10-21 remain pending but withdrawn from consideration. Accordingly, claims 22-49 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claim 1-6 have been rejected under 35 U.S.C. §103(a) as being obvious over Augart *et al.* (U.S. Patent No. 6,054,482) in view of Berge *et al.* (*J. Pharm. Sci*, 1977, 66:1-18). The applicants respectfully traverse.

The Augart *et al.* patent describes crystallized hydrochloride salt of 1-(aminomethyl)-cyclohexaneacetic acid (gabapentin). As acknowledged at page 2 of the Office Action, the Augart *et al.* patent does not disclose any of the organic acid salts of gabapentin recited in the currently pending claims, *i.e.*, tartaric acid, ethanedisulfonic acid, and maleic acid. The Office Action cites the Berge *et al.* publication for disclosing the advantage of pharmaceutically acceptable addition salts and a list of FDA approved salts, which includes hydrochloride, tartrate (tartaric acid), edisylate (ethanedisulfonic acid), and maleate (maleic acid). The Office Action indicates that one of ordinary skill in the art would have been motivated to prepare the claimed compounds in the recited salt form because they were generically approved by the Food and Drug Administration (FDA) to be desirable for commercial market.

Table 1 of the Berge *et al.* publication lists 53 anionic salts and 14 cationic salts, along with the relative frequency with which each salt type has been used, calculated as a percentage based on the total number of anionic or cationic salts in use through 1974. The applicants note that the Office Action does not assert that there is any structural similarity between gabapentin and the parent compounds listed in Table III of the Berge *et al.* publication, which lists "potentially useful salt forms of pharmaceutical agents". Thus, the only asserted motivation for combining the cited references lies in the physicochemical advantages of some salt forms and the fact that the salts

recited in the claims have been used over the years in conjunction with other drugs that were FDA-approved.

While it is true that identification of a salt form that imparts desirable physicochemical properties to a given class of parent compound would greatly benefit chemists and pharmaceutical formulators, only a limited number of generalizations are available to predict the effect of particular salt forms on the characteristics of a given drug (see page 1, column 2, and page 15, "conclusions" of Berge *et al.*). Such knowledge is simply not available with respect to gabapentin—and certainly not disclosed or suggested within the cited references. As the Berge *et al.* publication makes clear, the properties exhibited by a particular salt species of a parent compound are far from predictable, stating,

> choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound. Salt-forming agents are often chosen empirically ... Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles. (page 1, columns 1 and 2)

This unpredictability has not significantly improved since 1977, when the Berge et *al.* reference was published. Submitted herewith for the Examiner's consideration is the more recent Davies publication ("Changing the Salt, Changing the Drug", *The Pharmaceutical Journal*, 2001, 266:322-323). The Davies publication states,

> There is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity, and the supposition that the same salt form of two related parent compounds will behave in exactly the same way may not be correct. (emphasis added; page 322, column 1, paragraph 2)

> It is important to remember, however, that since changing the salt can dramatically change the properties of a drug, every salt form of a drug should be considered as a new medicinal product and tested appropriately before it is released for use in clinical practice. (page 323, last sentence)

It is clear from the foregoing that selection of an appropriate salt remains an empirical endeavor. The mere fact that tartaric acid, ethanedisulfonic acid, and maleic acid are salts that have been used over the years in conjunction with other FDA-approved drugs does not make it reasonable to infer that gabapentin salts formed therefrom would share similar properties with the hydrochloride salt of the drug. It is the properties and utilities that provide real world motivation for a person of ordinary skill in the art to make species structurally similar to those in the prior art. *In re Dillon*, 16 USPQ2d 1897, 1905 (Fed. Cir. 1990), *cert. denied*, 500 U.S. 904 (1991); *In re Stemniski*, 170 USPQ 343, 348 (CCPA 1971). Conversely, lack of any known useful properties weighs against a finding of motivation to make or select a species or subgenus. *In re Albrecht*, 185 USPQ 585, 587, 590 (CCPA 1975).

The Office Action also cites *In re Lemin*, 141 USPQ 814 (CCPA 1964) in support of its position. While it is true, generally speaking, that there is nothing unobvious in choosing "some" among "many" indiscriminately. The Office Action has not established that there is a reasonable expectation that any of the alternative salts provided in Berge *et al.*, other than hydrochloride, would work.

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness (see *In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) and the Office Action does not establish that one of ordinary skill in the art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the specifically recited organic acid salts from the lists of salts disclosed in *Berge et al.* The myriad of choices for salts provided by the Berge *et al.* publication affords no guidance for one of ordinary skill in the art to select the specifically recited salts of the claimed compounds and compositions. Further, the cited references do not teach interchangeability between hydrochloride salt and any of the three organic acid salts recited in the claims. A reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burckel*, 201 USPQ 67, 70 (CCPA 1979). The mere fact that it is possible to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render the compound obvious unless the art also contains something to suggest the desirability of the proposed combination. *In re Bergel*, 130 USPQ 206, 208 (CCPA 1961).

The Office Action cites no pertinent reference showing or suggesting to one of ordinary skill in the art to change the hydrochloride salt of Augart *et al.* to tartaric acid ethanedisulfonic acid, or maleic acid and, at best, in view of the cited references, one skilled in the art might find it obvious to try various combinations of gabapentin and FDA-approved salts listed in Berge *et al.* However, it is well settled that this is not the standard of 35 U.S.C. §103. Obviousness is not established by prior art which requires varying all parameters or trial of each of numerous possible choices until one possibly arrives at successful result, because such prior art gives no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful. *In re Geiger*, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). "Ought to be tried" is not the standard by which obviousness is determined.

It is only the applicants' specification teaching that when gabapentin and the recited organic acids are allowed to form salts, the resulting salts give rise to improved properties of the drug, particularly with respect to solubility properties, such as aqueous solubility and dose response properties. The mere fact that a prior art structure *might possibly* function as claimed or be modified in a way that would render the claims obvious does not render such claims obvious within the meaning of 35 U.S.C. §103. The governing standard is not whether a particular approach leading to an invention would be "obvious to try," but whether such an experiment would have been expected to succeed. *In re Merck & Co., Inc.*, 231 U.S.P.Q. 375, 379-80 (Fed. Cir. 1986). Applicants respectfully submit that there is no motivation in the prior art for combining the cited references to arrive at the claimed compounds and compositions with any reasonable expectation of success. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Claims 1-9 have been rejected under 35 U.S.C. §103(a) as being obvious over Augart *et al.* in view of Berge *et al.* and further in view of U.S. Pharmacopia #23 (National Formulary #18, 1995, pp. 1843-1844) and Rouhi (*Chem. Eng. News*, Feb. 2004, pp. 32-35). The applicants respectfully traverse.

The applicants' remarks set forth above in response to the foregoing rejection of claims 1-6 based on Augart *et al.* in view of Berge *et al.* are incorporated herein by reference in their entirety. There is no motivation in the prior art for combining the cited references to arrive at the claimed

compounds and compositions with any reasonable expectation of success. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 50-2626.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

August 23, 2005

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Attachment: Davies publication (*The Pharmaceutical Journal*, 2001, 266:322-323)

CHANGING THE SALT, CHANGING THE DRUG

By Glynis Davies, BSc, MRPharmS

Changing the salt form of a drug affects its clinical efficacy and safety. This article discusses the potential issues related to the use of different salts of drugs

Changing a drug from its free base or acid to a salt form is commonly done to improve its kinetics, absorption or physicochemical properties (eg, stability, hygroscopicity and flowability). Changing the salt form of a drug is a recognised means of modifying its chemical and biological properties without modifying its structure. Different salts of the same active drug are distinct products with their own chemical and biological profiles that underlie differences in their clinical efficacy and safety.

There is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity, and the supposition that the same salt form of two related parent compounds will behave in exactly the same way may not be correct. The literature contains many examples of salt forms that differ in the rate of absorption, toxicity and stability of the active drug.

SALT FORMATION

Salts are formed by the reaction of an acid with a base. Any compound with the characteristics of either an acid or a base can, in theory, form a salt, but whether or not a salt is formed depends on the relative strength of the acid or base. When a drug is formulated as a salt, the particular salt form determines the physiochemical properties of the product: stability, solubility and dissolution rate. These properties influence how the drug is handled by the body: how it is absorbed, distributed, eliminated and excreted. The biological activity of a drug at its target site depends not only on its structure and effect at that site, but also on how readily it can reach the site and how readily it is removed from it.

Selecting an appropriate salt form for a drug is an important factor in the early stages of new drug development.[1] The monoprotic hydrochlorides are the most frequent choice of anionic salt-forming radicals, with hydrochloride salts outnumbering sulphates by nearly six to one and forming the largest percentage of salts in use.[2] A decision to change the salt form at a later stage introduces the need to repeat toxicological, formulation and stability tests, with obvious implications for the overall development and production time for the new pharmaceutical product.

Once a drug has been marketed, there may be sound reasons for reformulating it in a different salt form to change its physicochemical properties. An example is provided by the analgesic propoxyphene, which was originally formulated as a hydrochloride salt. Propoxyphene was widely used in a fixed-dose combination with aspirin, but since aspirin proved to be unstable in close physical contact with propoxyphene hydrochloride, an additional step in the manufacturing process was needed to separate the two analgesics. When propoxyphene was reformulated as a napsylate salt, there was no problem of aspirin instability. The relative insolubility of the napsylate salt form compared with the hydrochloride was also an advantage, as it reduced the potential for parenteral abuse of propoxyphene.

Substitution of one salt form of a drug for another can also change the rate of absorption and other pharmacokinetic variables, as well as toxic potential and stability, and all these properties can affect the biological activity of a drug and the clinical use of the formulation.

RATE OF ABSORPTION

Salts differ in their solubility profiles and dissolution rates, which affect the rate of absorption of the drug and, in turn, the onset, duration, and intensity of its effect.[2] The bioavailability of a drug can therefore be modified by administering it in a different salt form. For example, a study of the relative bioavailability of the vasodilator naftidrofuryl in oxalate and citrate salt forms has shown that the relative rate of absorption is higher for the citrate than for the clinically used oxalate form of the drug.[3]

An example of salt substitution changing the intensity of biological response to a drug is again provided by propoxyphene. This established analgesic was first marketed in the United States in the form of a hydrochloride salt more than 40 years ago. When it was reformulated, the new napsylate salt form was found to have greater potency and a longer duration of action than the hydrochloride, attributable to differences in the rates of absorption of the two salt forms.[4,5] Another example of the variation in biological activity with salt form is provided by calcium preparations. Brand-name preparations, each containing a different calcium salt with a different absorption rate, are reported to vary significantly in their ability to suppress secretion of parathyroid hormone.[6] This has implications for their clinical use as calcium supplementation in osteoporosis.

Moving from clinical practice to veterinary medicine, a further example is provided by the anthelmintic pyrantel. The pamoate salt of pyrantel is reported to be three times as effective as the citrate against large bowel parasites, including resistant strains, because of its lower rate of absorption and consequently greater retention in the gastrointestinal tract.[7]

TOXICITY

Some cations and anions are known to be associated with toxic effects and will contribute to the intrinsic toxicity of the salt form. For example, lithium cations have no toxic effect in small quantities but when ingested in large amounts can cause irreversible damage to the kidney. Similarly, tartrate anions, which are usually absorbed only minimally from the gastrointestinal tract, can cause renal damage if they reach the circulation in high concentrations.[2] In addition, pravadoline maleate caused renal tubular lesions in the dog, as a result of maleic acid formed from the maleate anion.[8]

Changing the salt form of a drug can reduce its toxic potential. Typically, a salt that is slowly absorbed in the gastrointestinal tract is less toxic than one with a more rapid rate of absorption. For example, propoxyphene napsylate has an acute oral toxicity half that of propoxyphene hydrochloride when given to rats or mice in equimolar doses; this is due to the more gradual absorption of the napsylate.[9] Furthermore, in animal models, the napsylate appears to lack the convulsant properties of the hydrochloride.

Local irritancy Different salt forms can differ in their capacity to cause oesophageal irritation. For example, alprenolol in the form of the hydrochloride salt has an irritant effect on the oesophagus and can cause oesophageal ulceration in humans, whereas alprenolol benzoate has no irritant effects.[10] The difference in ulcerogenic potential has

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been related to the difference in solubility of the salts: alprenolol hydrochloride is highly water soluble and therefore may cause local damage due to local absorption, whereas alprenolol benzoate has low water solubility.

Different salt forms can also differ in the level of irritancy to the gastrointestinal tract, which may result in ulceration or bleeding. Nitrate anions are known to cause local irritancy to the gastrointestinal tract leading to nausea and gastric distress.[2] Lithium salts irritate the gastrointestinal mucosa, an effect due predominantly to the anion moiety rather than the lithium cation. The effect is more marked, with greater discomfort to the patient, the greater the amount of anion administered.[11]

Reaction products Different salt forms of a drug can differ in toxicity because of reaction products in their manufacture. Reaction between the cation or anion moiety of the salt and impurities associated either with the active drug or arising from the manufacturing process can result in the formation of toxic products. For example, formic acid has relatively low intrinsic toxicity, but its salts are often contaminated with highly toxic methyl and ethyl formate esters, which are reaction-solvent side products.[12]

Stability

The particular salt form of a drug can affect its stability. For example, the stability of a drug formulated for administration as tablets can be affected by the hygroscopicity of the salt form. Salts of mineral acids such as hydrochlorides, sulphates and methane sulphonates are highly polar. The polar ionised groups exposed on crystal surfaces create a highly hydrophilic surface favouring wettability and leading to hygroscopicity.[13] In turn, this can reduce stability, particularly if the drug is susceptible to hydrolytic degradation.

Stability is also influenced by the hydrophobicity of the salt-forming acid. The formation of salts with low water solubility is a means of increasing the chemical stability of a drug that is sensitive to heat and moisture, such as xilobam. Stability is an issue for xilobam tablets containing the highly soluble sulphate salt of the drug, because the salt is readily hydrolysed and dissolves in surface moisture. However, when the salt-forming acid is aryl sulphonic acid, the hydophobic aryl group presents a barrier to dissolution and this salt form of xilobam is more stable when exposed to high temperature and humidity.[14]

Thermal stability can vary from one salt form of a drug to another. For example, the hydrochloride salt of lincomycin undergoes thermal degradation whereas the cyclamate is significantly more stable.[15] Similarly, the procaine salt of penicillin G has good aqueous stability but poor thermal stability, unlike sodium or potassium salts of the antibiotic, which can withstand prolonged exposure (four days) to temperatures of 100C.[16]

Conclusion

Different salt forms of a drug differ in ways that can impact on their clinical efficacy and safety. Changing the salt form varies the solubility and rate of dissolution of a drug, which in turn affects its bioavailability, pharmacokinetic profile, toxicity, and chemical stability. Early selection of an appropriate salt form in the development of a new drug will influence the timely completion of drug development and production, an important factor in accelerating the process of drug discovery.

Substitution of one salt form for another can accelerate the onset and duration of biological activity of a drug and is a recognised means of reducing its toxic potential or improving its chemical stability. It is important to remember, however, that since changing the salt can dramatically change the properties of a drug, every salt form of a drug should be considered as a new medicinal product and tested appropriately before it is released for use in clinical practice.

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